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Evaluation of Changes in Serum Insulin-Like Growth Factor-1 and Insulin-Like Growth Factor Binding Protein 3 in Children with Adenotonsillar Hypertrophy Before and After Surgery

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Circulating concentrations of Insulin-Like Growth Factor-1 (IGF-1) and Insulin-Like Growth Factor Binding Protein 3 (IGFBP3) are strongly related to diurnal GH secretion, reflecting mean daily serum GH levels. This interventional experiment studied serum levels of IGF-1 and IGFBP3 of 30 boys of 3-8-years old with grade 3 and 4 adenotonsillar hypertrophy before and after adenotonsillectomy (T and A surgery). Fasting levels of serum growth hormone biochemical markers (IGF-1 and IGFBP3) were measured on the morning of T and A surgery and 4-5 months postoperatively. IGF-1 and IGFBP3 serum levels were significantly increased in these patients after T and A surgery ($p < 0.01$). Therefore Grade 3 and 4 adenotonsillar hypertrophy could be considered as major factors for prompts reduction of both IGF-1 and IGFBP3.

Key words: Adenotonsillar hypertrophy, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP3), adenotonsillectomy

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INTRODUCTION

Upper airway obstruction due to adenotonsillar hypertrophy (ATH), especially in cases accompanied by obstructive sleep apnea syndrome (OSAS), causes various difficulties such as neurobehavioral and cardiopulmonary consequences, nocturnal enuresis, as well as growth retardation (Rosen and Haddad, 2000; Chan *et al.*, 2004; Lipton and Gozal, 2004; Young *et al.*, 2002). The occurrence of lymphatic tissue growth that may be observed between the ages of 2 and 5 (Rosen and Haddad, 2000) or 2 to 8 years (Chan *et al.*, 2004; Nieminen *et al.*, 2002) is the primary cause of OSAS. Based on available statistics, the possibility of snoring occurring in children is 3% to 12% and can be as high as 20% in habitual snorers (Chan *et al.*, 2004; Nieminen *et al.*, 2002). However, OSAS has been reported in 1 to 10 percent of children (Rosen and Haddad, 2000; Chan *et al.*, 2004; Lipton and Gozal, 2004; Young *et al.*, 2002) and the possibility of growth retardation or failure to thrive (FTT) occurring in these children (Rosen and Haddad, 2000; Chan *et al.*, 2004; Lipton and Gozal, 2004) has also been reported to be more than 50 % in preliminary reports (Lipton and Gozal, 2004).

Nowadays through better knowledge of this syndrome and its timely treatment, the statistics have markedly decreased and adenotonsillectomy (T and A) is curative in most patients (Lipton and Gozal, 2004; Chan *et al.*, 2004). With regard to the occurrence of growth disruption phenomena in children affected by ATH and OSAS, various explanations such as dysphagia, anorexia, increased work of breathing during sleep, hypoxia or acidosis as well as the disruption in the secretion of growth hormone (GH) and type 1 insulin-like growth factor (IGF-1 and IGFBP3) have been suggested (Rosen and Haddad, 2000; Chan *et al.*, 2004; Lipton and Gozal, 2004).

Most of the circulating IGF-1 is transferred by attaching itself to a carrier protein called insulin-like growth factor binding protein 3 (IGFBP-3). Since, the serum levels of IGF-1 and IGFBP-3 depend on the serum level of GH; these factors are used as biochemical markers to evaluate GH secretion in these types of studies (Nieminen *et al.*, 2002).

Various studies reported that airway obstruction and sleep apnea syndrome due to adenotonsillar hypertrophy (ATH) disrupt the normal process of growth by causing hypoxemia, reduction of nocturnal GH secretion, respiratory acidosis, increased work of breathing during sleep and numerous other symptoms (Rosen and Haddad, 2000; Chan *et al.*, 2004; Lipton and Gozal, 2004).

Nieminen *et al.* (2002) reported that serum levels of IGF-1 and IGFBP-3 were below the normal level in children affected by severe ATH.

Although the relation between ATH and growth disruption is mentioned by others, but a definitive and clear confirmation of the relation between GH and GH biochemical markers (IGFBP3-IGF-1) secretion changes before and after T and A is not confirmed yet (Rosen and Haddad, 2000; Melmed, 2001; Sterni and Tunkel, 1998). So in this study we decided to evaluate the GH biochemical markers (IGF-1, IGFBP3) factors in children who had been qualified for T and A surgery. Our data were based only on interviews conducted with the patient's parents, because PSG is very expensive (250 US \$) and is not cost effective.

MATERIALS AND METHODS

This study was an interventional experiment conducted in 2005. Subjects were selected from patients who had been admitted by ENT Clinic of Shafa Hospital affiliated with the Medical College of Kerman Medical Sciences University in Iran. Patients included in the study were 3-8 years old boys. They were selected based on their individual conditions, the results of physical examinations, the presence of grade 3 and 4 ATH and their parents' interview comments indicating the presence of airway obstruction. Informed consent was taken from the parent's patients before conducting patient examinations and blood sampling. A second blood sample was taken 120 to 150 days after performing the operation. The same laboratory measurement procedure was used before and after surgery.

Radiography of a semi-extended neck profile was done for all patients to evaluate the condition of their respective adenoids. In addition so as to further identify any disruptive factors, all patients were examined for other prevailing systemic conditions such as hypothyroidism, diabetes mellitus, rheumatoid arthritis, liver and heart ailments, or any chronic infections. Individuals with any suspicious conditions were accordingly excluded from the study.

Finally, 31 patients between 3 and 8-years of age were selected for the initial study group. To measure IGF-1 and IGFBP3 levels, fasting blood samples were obtained at 6 AM and serum were separated and stored at -20°C. Routine laboratory tests such as complete blood count (CBC), prothrombin time (PT) and partial prothrombin time (PTT) were also conducted before surgery and results were subsequently evaluated. Test results were normal for all patients.

IGFBP3 (Orlon Diagnostica Spectra, Finland) level was measured using radioimmunoassay (RIA) with 0.6 mIU L⁻¹ sensitivity while IGF-1 (Immunotech Laboratory Kits, France) level measurements were taken using immunoradiometric assay (IRMA). Follow-up measurements were taken 120 to 150 days later because the half life of IGF-1 is long and a period of at least three months is necessary to allow for the development of observable changes. In addition, surgery causes reduced IGF-1, IGFBP3 secretion. Accordingly, this time lapse is needed to assure elimination of disruptive factors. Finally, postoperative pain typically delays the resumption of the patient's normal food intake.

At the appointed follow-up time, only 30 of the original 31 patients originally selected for the study returned for evaluation and sampling. Considering the number of calculated sample value of 28 patients, this number seemed adequate to make a proper evaluation. Accordingly, the test results of these 30 patients were statistically analyzed.

RESULTS

Table 1 shows that most of the patients (70%) with ATH were in fourth degree (75-100%) of airway obstruction.

Table 2 shows the pattern of IGF-1 and IGFBP3 serum levels after T and A surgery. As the data shows after T and A surgery 76.6% (23) of patients had normal or above normal of IGF-1 and IGFBP3 serum levels, compared to 20% before T and A surgery irrespective of concurrent consideration of the degree of enlarged tonsils and adenoids.

Also there was a significant increase in IGF-1 and IGFBP3 serum levels during 120-150 day after T and A surgery as compared to pre-operative values and approximately 100% increase in IGF-1 and IGFBP3 serum levels has been observed compared to pre-operative values (Table 3) ($p < 0.01$).

Table 1: Pattern of largeness of tonsils and adenoid sizes in children with adenotonsillar hypertrophy (ATH) before T and A surgery

Degree of largeness of tonsils	No.	Percentage
Third degree (50-75% of airway obstruction)	9	30
Fourth degree (75-100% of airway obstruction)	21	70
Total	30	100

Table 2: Demographic distribution of serum levels of IGF-1 and IGFBP3 in children with adenotonsillar hypertrophy before and after T and A surgery

No. of patients	Below normal	Normal and above normal
Before surgery		
30	24 (80%)	6 (20%)
After surgery		
30	7 (23.3%)	23 (76.6%)

Table 3: Serum levels changes of IGF-1 and IGFBP3 in children with adenotonsillar hypertrophy (ATH) before and after T and A surgery

Variables	Before operation	After operation	Test results
IGF-1(IU L ⁻¹) (n = 30)	109.7±60.9	262.8±84	$p < 0.01$
IGFBP3(IU L ⁻¹) (n = 30)	1851.0±464.4	3240.0±731	$p < 0.01$

Table 4: Clinical symptoms observed in children with adenotonsillar hypertrophy (ATH) before and after T and A surgery

Symptoms	Before surgery		After surgery	
	Present (%)	Absent (%)	Present (%)	Absent (%)
Night snoring	90.0	10.0	3.3	96.7
Open mouth sleeping	96.7	3.3	86.7	13.3
Stop breathing in sleep	100.0	0.0	0.0	100.0
Dysphagia	23.4	76.6	0.0	100.0
Nocturnal enuresis	6.7	93.3	0.0	100.0
Daytime sleepiness	3.3	96.7	0.0	100.0
Hyponasal speech	20.0	80.0	0.0	100.0
Frequent night waking	76.7	23.3	0.0	100.0
Earache	20.0	80.0	0.0	100.0
Hearing loss	16.7	83.3	3.3	96.7

Changes in the patient's clinical symptoms before and after operation were clearly noticeable. Not only was the nocturnal breathing disruption corrected in all patients, but their other difficulties such as dysphagia, nocturnal enuresis, daytime sleepiness, hyponasal speech, frequent waking and earache were also almost completely resolved after T and A surgery. Night snoring and open mouth sleeping were also observed to be significantly improved (Table 4).

DISCUSSION

The results of this study shows that after T and A surgery 76.6% (23) of patients had normal or above normal of IGF-1 and IGFBP3 serum levels, compared to 20% before T and A surgery irrespective of concurrent consideration of the degree of enlarged tonsils and adenoids and results are in complete agreement with other reports (Nieminen *et al.*, 2002; Yilmaz *et al.*, 2002; Selimoglu *et al.*, 2003; Bar *et al.*, 1999; Straddling *et al.*, 1990; Williams *et al.*, 1991). This means that number of 6 individuals in our study with normal and above normal IGF-1, IGFBP3 levels before T and A increased dramatically to 23 after T and A surgery. Correspondingly, the number of the 24 children with low IGF-1, IGFBP3 levels before T and A surgery was significantly reduced to 7 postoperatively. The increase in IGF-1 and IGFBP-3 serum levels following A and T surgery in patients with ATH is reported by other investigators (Yilmaz *et al.*, 2002).

Yilmaz *et al.* (2002) observed a statistically significant increase in the IGF-1 and IGFBP-3 serum levels of 32 patients after surgery ($p < 0.001$). It is noteworthy that in 7 of the 32 qualified children in their

study, the preoperative IGF-1 level was below normal. However, this level showed a statistically significant increase ($p = 0.016$) after surgery (Yilmaz *et al.*, 2002; Nieminen *et al.*, 2002).

Selimoglu *et al.* (2003) reported that the lower caloric intake either due to anorexia, dysphagia, or GH secretion inhibition or even a combination of these, may be the cause of failure to thrive (FTT) in ATH-afflicted children.

Bar *et al.* (1999) also reported the improvement in height, weight, IGF-1 as well as breathing difficulty indices and sleep anomalies in OSAS-afflicted children through overnight polysomnography (PSG), however, no significant change in IGFBP-3 serum levels was evident which is not in agreement with the result of present study. But Nieminen *et al.* (2002) reported significant increases of circulating IGF-1 and IGFBP-3 in 17 of 19 children who underwent surgery.

The results of the present study showed significant improvement in clinical symptoms (dysphagia, nocturnal enuresis, daytime sleepiness, hyponasal speech, snoring, numerous breathing delays, open mouth sleeping, frequent night waking) of affected boys postoperatively, which is in complete agreement with the results of other investigators (Straddling *et al.*, 1990; Williams *et al.*, 1991; Marcus *et al.*, 1994).

In summary, the results of this study showed that IGF-1, IGFBP3 serum levels in children with grade 3 and 4 tonsils and adenoids were below normal level before surgery and were increased significantly in patient undergoing T and A procedures. Significant clinical improvement of snoring, numerous breathing delays, open mouth sleeping, frequent night waking was observed in ATH affected patients. Therefore, the presence of night snoring and numerous breathing delays in patients having grade 3 and 4 tonsils and adenoids must be considered as an definite indication for the need for surgical remedy. Also this study confirms that T and A is a highly effective curative treatment for ATH.

REFERENCES

- Bar, A., A. Tarasiak, Y. Segev, M. Phillip and A. Tal, 1999. The effect of adenotonsillectomy on serum insulin-like growth factor-1 and growth in children with obstructive sleep apnea. *J. Pediatr.*, 135 (1): 76-80.
- Chan J., J.C. Edman and P.J. Koltai, 2004. Obstructive sleep apnea in children. *Am. Fam. Physician*, 69 (5): 1147-1154.
- Lipton, A.J. and D. Gozal, 2006. Obstructive sleep apnea syndrome. *Emedicine from Web MD*. Last updated, pp: 1-16.
- Marcus, C.L., J.L. Carroll, C.B. Koerner, A. Hamer, J. Lutz and G.M. Loughlin, 1994. Determinants of growth in children with the obstructive sleep apnea syndrome. *J. Pediatr.*, 125 (4): 556-562.
- Melmed, S., 2001. Disorders of the Anterior Pituitary and Hypothalamus. In: *Harrison's Principles of Internal Medicine*, Braunwald, E., A.S. Fauci, D.L. Kasper, F.L. Hauser, D.L. Longo and J.L. Jameson (Eds.). McGraw-Hill, New York, 2: 2029-2052.
- Nieminen, P., T. Lopponen, U. Tolonen, P. Lanning, M. Knip and H. Lopponen, 2002. Growth and biochemical markers of growth in children with snoring and obstructive sleep apnea. *Pediatrics*, 109 (4): e55-61.
- Rosen, C.L. and G.G. Haddad, 2000. Obstructive Sleep Apnea and Hypoventilation in Children. In: *Nelson's Textbook of Pediatrics*, Behrman, R.E., R.M. Kliegman and H.B. Jenson (Eds.). Philadelphia, WB Saunders, 1: 1268-1271.
- Selimoglu, E., M.A. Selimoglu and Z. Orbak, 2003. Z: Does adenotonsillectomy improve growth in children with obstructive adenotonsillar hypertrophy? *J. Int. Med. Res.*, 31 (2): 84-87.
- Sterni, L.M. and D.E. Tunkel, 1998. Obstructive Sleep Apnea. In: *Otolaryngology and Head and Neck Surgery*, Cummings, C.W., J.M. Frederickson, C.J. Krause, L.A. Harker, D.E. Schuller and M.A. Richardson (Eds.). St. Louis, Mosby, 3: 216-228.
- Straddling, J.R., G. Thomas, A.R.H. Warley, P. Williams and A. Freeland, 1990. Effect of adenotonsillectomy on nocturnal hypoxaemia, sleep disturbance and symptoms in snoring children. *Lancet*, 335 (3): 249-253.
- Williams, E.F., P. Woo, R. Miller and R.M. Kellman, 1991. The effects of adenotonsillectomy on growth in young children. *Arch. Otolaryngol. Head Neck Surg.*, 104 (4): 509-516.
- Yilmaz, M.D., A.S. Hosal, H. Oguz, N. Yordam and S. Kaya, 2002. The effects of adenotonsillectomy on serum IGF-1 and IGF-BP3 levels in children. *Laryngoscope*, 112 (5): 922-925.
- Young, T., P.E. Peppard and D.G. Gottlieb, 2002. Epidemiology of obstructive sleep apnea: A population of health perspective. *Am. J. Respir. Crit. Care Med.*, 165 (9): 1217-1239.